(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 August 2001 (30.08.2001)

PCT

(10) International Publication Number
WO 01/62282 A2

(51) International Patent Classification[7]: A61K 39/39, 39/00, A61P 37/04

(21) International Application Number: PCT/GB01/00816

(22) International Filing Date: 26 February 2001 (26.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0004530.2 25 February 2000 (25.02.2000) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/62282 A2

(54) Title: ADJUVANTS

(57) Abstract: Vaccine compositions comprise an adjuvant capable of reducing T-helper cell type-1 responses and enhancing T-helper cell type-2 responses. The adjuvant preferably comprises a homoserine lactone.

ADJUVANTS

Field of the Invention

This invention relates to adjuvants for vaccines.

Background of the Invention

Vaccines are a powerful tool in modern medical practice. They provide an effective, cost-efficient, method of preventing disease, and may also be used to stimulate the immune system in response to an existing infection. Modern vaccines are being developed to ensure enhanced immune responses to infection. Typically, vaccines require co-administration with an adjuvant.

Adjuvants are stimulants used with specific antigens in vaccine compositions to induce powerful and disease-appropriate immune responses to the vaccine.

They are often materials derived from bacterial extracts. For example, mycobacterial antigens are routinely used to boost cell-mediated immunity as a component of Freund's complete adjuvant. Similarly, extracts from *Corynebacterium parvum* and *Bordetella pertussis* are commonly used.

Part of the immune response includes a T-helper cell response, of which there are two types. T-helper 1 (Th1) cells secrete interleukin 2 (IL-2) and γ-interferon, leading to an activation of cytotoxic T-cells and macrophages. T-helper 2 (Th2) cells secrete IL-4 and IL-5, which assist B cells and eosinophils.

N-acyl homoserine lactones have been isolated from a number of bacteria, such as *Photobacterium (Vibrio) fischeri*, *Pseudomonas aeruingosa*, *Erwinia carotovora*, *Agrobacterium tumefaciens* and others from the *Serratia*, *Enterobacter* and *Yersinia* genera. The immunogenic effect of one such AHL, N-(3-oxododecanoyl)-L-homoserine lactone (OdDHL), is illustrated in Telford *et al*, Infection and Immunity, 1998; 66(1):36-42.

Summary of the Invention

The present invention is based on the realisation that a T-helper 1 (Th1) response to vaccine compositions is not always appropriate, and that a T-helper 2 (Th2) response is preferable in some cases.

According to the present invention, a vaccine composition comprises an active agent (immunogen) and an adjuvant, wherein the adjuvant is capable of reducing T-helper cell type-1 responses and enhancing T-helper cell type-2 responses.

According to a second aspect of the invention, the adjuvant described above is used in the manufacture of a vaccine composition for the prevention or treatment of infection.

According to a third aspect of the invention, a homoserine lactone is used in the manufacture of a composition for oral administration with an active agent, to induce oral tolerance to the active agent.

Description of the Invention

The adjuvants used in the present invention comprise compounds that are capable of reducing T-helper cell type-1 responses and enhancing T-helper cell type-2 responses. Although specific compounds that have these effects are provided in the specification, it is possible for the skilled person to identify further compounds by testing compounds for the desired effects. With knowledge of an appropriate test, it is possible for the skilled person to use conventional combinatorial chemistry-based approaches to identify further compounds that may have activity in the adjuvant compositions.

The adjuvants of the invention promote the T-helper 2 response. This may be characterised by measuring IgG1 in the presence of the adjuvant of the invention, and comparing this to that obtained using alum or phosphate buffered saline as the adjuvant. The adjuvants also reduce the T-helper 1 response in comparison to that observed for the same immunogen using alum or phosphate buffered saline

as the adjuvant. The T-helper 1 response may be characterised by measuring IgG2a.

A preferred embodiment of the invention is the use of N-acyl homoserine lactones (AHL) in the adjuvant compositions. The use of OdDHL is most preferred.

OdDHL suppresses tumour necrosis factor α (TNFα) and interleukin-12 (IL-12) production by macrophages, leading to a reduction in Th1 cell responses. Further, IgG1 and IgE responses, in murine and human tissue cultures, respectively, are promoted.

The adjuvants may be prepared for separate or co-administration with the vaccine. Preferably, the adjuvant and vaccine are co-administered in the one composition.

The vaccine may be any appropriate vaccine for the treatment/prevention of a particular disease, in particular any disease for which an enhanced Th2 response is desirable. In a further preferred embodiment, the disease is a nematodal infection or a trypanosomal infection, e.g. infection by *Necator americanus*.

The vaccine may be prepared by techniques known in the art. Appropriate immunogens will also be known to those skilled in the art. Immunogens may be of any suitable biological material that is capable of eliciting the appropriate immune response. The immunogen may be an attenuated microorganism or a protein or peptide fragment of sufficient size to generate the unique immune reaction against an infecting agent. Alternatively, the immunogen may be an antibody, e.g. a monoclonal antibody, raised against an appropriate antigen.

Vaccines for hookworm infections are disclosed in Sen *et al.*, Vaccine, 2000; 18:1096-1102, in Ghosh *et al.* The Journal of Infectious Diseases, 1999; 180:1674-1681, and in Taylor *et al.*, J. Exp. Med., 2000; 191(8):1429-1436.

The type and concentrations of the vaccine and the adjuvant may be readily determined by a person skilled in the art. For example, the composition may comprise 10 mg/ml of a vaccine and 100 μM homoserine lactone in the

adjuvant, together with a pharmaceutically acceptable diluent. Typically, concentrations of vaccine will be in the range comprising of 10 mg - 10 μg/ml, and the adjuvant may be in the range of 10-100 μM. Acceptable diluents will be known to the skilled person, based on conventional adjuvant formulations.

The vaccine may be administered by any convenient means, in particular, by oral, systemic or parentoral routes, or a combination of these. For example, it is now established that tolerance to the systemic administration of certain drugs may be enhanced by first administering the drug through the oral route. Oral tolerance may therefore be desirable in the present invention in the treatment of autoimmune disorders, where a patient's immune system is attacking self-antigens. In this aspect, the administration of a homoserine lactone compound together with autoantigens, via the oral route, may induce tolerance to the autoantigens, resulting in reduced severity of the autoimmune disorder. For example the treatment may comprise collagen or myelin proteins as the autoantigen, to treat rheumatoid arthritis and multiple sclerosis, respectively. However, the induction of oral tolerance may be desirable for any protein-based therapy, e.g. antibody therapy. The homoserine compounds may therefore induce tolerance to antibodies, thereby enhancing their therapeutic efficacy.

CLAIMS

1. A vaccine composition comprising an active agent and an adjuvant, wherein the adjuvant is capable of reducing T-helper cell type-1 responses and enhancing T-helper cell type-2 responses.

2. A composition according to claim 1, wherein the adjuvant comprises a homoserine lactone.

3. A composition according to claim 1, wherein the adjuvant comprises N-(3-oxododecanoyl)-L-homoserine lactone.

4. A composition according to any preceding claim, for use in therapy.

5. Use of a compound capable of reducing T-helper cell type-1 responses and enhancing T-helper cells type-2 responses as an adjuvant in the manufacture of a vaccine for the prevention or treatment of infection.

6. Use according to claim 5, wherein the vaccine is for the treatment of a nematodal infection or a trypanosomal infection.

7. Use according to claim 5 or claim 6, wherein the compound is a homoserine lactone.

8. Use of a homoserine lactone in the manufacture of a composition for oral administration with an active agent, to induce oral tolerance to the active agent.

9. Use according to claim 8, wherein the active agent is a protein or peptide.

10. Use according to claim 8 or claim 9, wherein the active agent is an autoantigen.

11. Use according to claim 8 or claim 9, wherein the active agent is an antibody.

12. Use according to any of claims 7 to 11, wherein the homoserine lactone is N-(3-oxododecanoyl)-L-homoserine lactone.